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19. ABSTRACT (Continue on reverse if necessary and identify by block number) <p>This research has been aimed at understanding basic mechanisms of neuronal communication in the mammalian brain. The work has focused on rapid mechanisms of electrical and synaptic transmission with an emphasis on local circuits. Much of our research has dealt with electrical interactions between hippocampal neurons, but recently we have also studied mechanisms of excitatory and inhibitory synaptic transmission in the hypothalamus.</p> <p>In the hippocampus, alterations in the osmolality of the extracellular fluid greatly modified the synchronous bursts of population spikes that occur in low Ca^{2+} solutions (i.e., with chemical synapses blocked). Increases in osmolality reduced or blocked the spontaneous bursts, and decreases in osmolality had the opposite effect. Since these changes in osmolality (10-20%) would be expected to cause cell shrinkage or swelling, modifications in the strength of ephaptic transmission probably mediate or contribute significantly to these effects. (CONTINUED).</p>						
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kynurenic acid; NMDA receptors; local circuits; supraoptic nucleus; paraventricular nucleus; Delta suprachiasmatic nucleus; hypothalamus

ABSTRACT (Section 19 of DOCUMENT PAGE - Continued)

Studies in the hypothalamus have primarily addressed the role of excitatory amino acids (EAAs) in fast synaptic transmission in the supraoptic and paraventricular nuclei. Kynurenic acid and delta-L-glutamylglycine (broad-spectrum EAA antagonists) reduced EPSPs in supraoptic neurons, while N-methyl-D-aspartate (NMDA) antagonists had relatively little effect on EPSPs. Other studies showed that kynurenic acid had dose-dependent effects on EPSPs of at least two types of paraventricular neurons. Similar actions were also seen on synaptic currents studied with the single-electrode voltage-clamp (SEVC) technique. Pilot studies suggested that intracellular recording from suprachiasmatic neurons should be feasible, which may allow us in the future to test hypotheses about the role of amino acid transmitters in this nucleus.

We have initiated studies on local synaptic circuits among hypothalamic neurons. Using glutamate microstimulation, evidence of a local inhibitory input (probably GABA-ergic) to paraventricular neurons was found. It should thus be possible to study synaptic interactions within and among the paraventricular and suprachiasmatic nuclei, the two hypothalamic regions most involved in stress responses and circadian mechanisms.

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1. RESEARCH OBJECTIVES

Our overall research objective has been to understand mechanisms responsible for rapid communication between central mammalian neurons and to learn fundamental processes responsible for regulating these neuronal interactions. Recent work in the hippocampus has involved electrical field effects (ephaptic transmission) and their possible synchronizing actions. Although electrical interactions have direct relevance to certain disease states, such as epilepsy, they are probably also involved in information processing in the normal brain. A critical issue that we have sought to address is whether this form of interaction can be consistently altered by experimental treatments.

Another area of research concerns mechanisms of synaptic transmission in the mammalian hypothalamus. The magnocellular neuroendocrine system (i.e., paraventricular and supraoptic nuclei with their oxytocinergic and vasopressinergic neuroendocrine cells) has long served as a model system for the study of hypothalamic function. It is well known that the paraventricular nucleus contains neuroendocrine cells that secrete corticotrophic releasing hormone (CRH), which controls secretion of other hormones that mediate the stress response. The suprachiasmatic nucleus, which is near these nuclei, regulates circadian rhythms. A major objective is to determine whether excitatory amino acids play a role as neurotransmitters in these hypothalamic nuclei. The primary method has been to examine the effects of EAA antagonists on EPSPs of hypothalamic neurons. Finally, another objective is to ascertain the types of local neuronal interactions that occur in and among these hypothalamic nuclei.

2. STATUS OF THE RESEARCH

- A. Effects of alterations in osmolality of low- $[Ca^{2+}]$ solutions on synchronous bursting of hippocampal neurons: Evidence for an important role of ephaptic transmission.

Reductions in extracellular $[Ca^{2+}]$ not only block synaptic transmission of CA1 pyramidal cells, but also increase excitability and lead to spontaneous bursts of population spikes (Jefferys and Haas 1982, Taylor and Dudek 1982, Konnerth, Heinemann, and Yaari 1984). Thus, chemical synaptic transmission is not necessary for burst synchronization by these neurons. Because the number and strength of electrotonic junctions estimated for the hippocampus appear to be too low to synchronize the bursts alone (e.g., Traub, Dudek, Taylor, and Knowles 1985), shifts in the concentration of extracellular ions (particularly K^+) combined with electrical field effects (ephaptic transmission) are thought to play an important role in synchronization of hippocampal neurons.

Although low- $[Ca^{2+}]$ solutions readily block synaptic responses to single stimuli, Konnerth and Heinemann (1983) showed that repetitive stimulation could lead to frequency facilitation of synaptic responses. Most earlier work with low- $[Ca^{2+}]$ solutions and synchronous bursting has not reported whether synaptic transmission was blocked to repetitive stimulation. Although this facilitation could not account for synchronization of the early spikes in a spontaneous burst, it could contribute to synchrony later in the burst. We have studied spontaneous bursts of population spikes under conditions when synaptic transmission was also blocked to repetitive stimulation.

If changes in the concentration of extracellular ions (such as K^+) and electrical field effects synchronize hippocampal neurons, alteration of solute concentration in the extracellular medium (i.e., osmolality) using membrane-impermeant molecules should cause

swelling or shrinkage of neurons and glia, and thus influence the degree of synchronization by modifying extracellular resistance. We have used low- $[Ca^{2+}]$ solutions where synaptic transmission was demonstrably blocked to both single and repetitive pulses to test the hypothesis that alterations in the osmolality of the medium (and associated changes in the extracellular space and resistance) predictably modify the occurrence of synchronous population spikes. Slices of rat hippocampus were exposed to zero- $[Ca^{2+}]$ solutions with EGTA (1-2 mM) to block chemical synaptic responses and induce spontaneous bursts of population spikes. Synaptic transmission of CA1 neurons in 3 mM K^+ to stimulation of the Schaffer collateral/commissural pathway was rapidly blocked with either single or repetitive pulses (up to 25 Hz for 20 sec). When $[K^+]$ was raised to 5 mM, negative shifts with or without population spikes occurred in the CA1 area. These experiments confirm that lowering of extracellular $[Ca^{2+}]$ (plus addition of EGTA), where chemical synaptic transmission is blocked not only to single pulses but also to repetitive stimulation, leads to synchronous bursting. Thus, synaptic transmission is unlikely to be involved in synchronization of these events in either the early or late periods of the bursts.

When slices exhibiting spontaneous bursts of population spikes in low- $[Ca^{2+}]$ media were exposed to solutions of increased osmolality (5-40 mOsm/kg mannitol or sucrose), the bursts of spontaneous population spikes were dramatically reduced or entirely blocked. The effects of increased osmolality were usually reversible. Similar exposure of hippocampal slices to low- $[Ca^{2+}]$ solutions containing the membrane-permeant solute, glycerol (5-40 mOsm/kg), had little or no effect on synchronous bursts of population spikes in the CA1 area. In those hippocampal slices that showed negative shifts without population spikes in the low- $[Ca^{2+}]$ solutions, reduction of the osmolality of the extracellular fluid by addition of water (5-20%, 10-60 mOsm/kg) or reducing the concentration of NaCl (10-20 mM) frequently induced bursts of population spikes on the peaks of the negative shifts. This effect was also usually reversible. In some preparations that showed neither negative shifts nor negative shifts with population spikes in the low- $[Ca^{2+}]$ solution, similar exposure to dilute media could induce negative shifts and occasionally population spikes. The blocking effects of membrane-impermeant solutes, such as mannitol and sucrose, on spontaneous bursting could be reversed by application of dilute medium. Conversely, when application of dilute medium induced spontaneous population spikes superimposed on negative shifts, solutions containing mannitol or sucrose could reversibly block the population spikes.

The observation that increased osmolality of the extracellular fluid with membrane-impermeant solutes, but not with membrane-permeant solutes, blocks the spontaneous bursts of population spikes argues that reductions in extracellular space decrease synchronization by altering non-synaptic mechanisms. The converse result that dilute media increases the propensity of hippocampal slices to fire spontaneous bursts of population spikes suggests that cellular swelling and a reduction in the extracellular space enhances synchronization through non-synaptic mechanisms. These data strongly support the hypothesis that changes in the concentration of extracellular ions (such as K^+) and electrical field effects (ephaptic transmission) play an important role in synchronizing hippocampal neurons.

B. Pharmacological evidence that excitatory amino acids (EAAs) mediate fast synaptic transmission in the hypothalamus

The magnocellular neuroendocrine system, which is responsible for secretion of the peptide hormones oxytocin and vasopressin, is located in the paraventricular and supraoptic nuclei of the hypothalamus. These nuclei represent one of the best studied neuroendocrine systems in mammals, and their peptide hormones are known to be intimately involved in a wide range of homeostatic mechanisms. These hormones may act as neuromodulators in the

brain to promote learning and memory. In addition, the paraventricular nucleus contains neuroendocrine cells that secrete corticotropin releasing hormone (CRH), which indicates that this system is intimately involved in responses to stress. This region is also the main target of afferents from the suprachiasmatic nucleus, thus suggesting a crucial role in circadian modulation of the endocrine system and autonomic nervous system. The studies described below, partially also supported by small grants from other sources, were aimed at understanding basic mechanisms of neurotransmission and local synaptic circuits in these hypothalamic nuclei.

1. Supraoptic nucleus

Intracellular recordings from magnocellular neurons in the supraoptic nucleus were obtained from rat hypothalamic slices in order to determine the effects of specific transmitter antagonists on evoked PSPs, action potential afterdischarge, and spontaneously occurring PSP's. Broad-spectrum EAA antagonists, kynurenic acid and δ -D-glutamylglycine, significantly reduced or eliminated electrically evoked depolarizing PSPs and spike discharges. These compounds also greatly reduced the amplitude and apparent frequency of spontaneous PSPs. Under these experimental conditions, the specific NMDA-receptor antagonist, D,L-2-amino-5-phosphonopentanoic acid (AP5), did not significantly reduce these measures of synaptic activation. The δ -aminobutyric acid (GABA) antagonist, bicuculline methiodide, reduced some PSP's when the cells were hyperpolarized (-75 to 80 mV) with steady injected currents; kynurenic acid antagonized bicuculline-resistant PSPs. The involvement of a hypothetical cholinergic input to the supraoptic nucleus in the responses to stimulation of the dorsolateral region was tested by bath application of nicotinic cholinergic antagonists, particularly d-tubocurarine. Nicotinic antagonists, even after prolonged exposure to high concentrations, did not reduce the responses of supraoptic neurons to dorsolateral stimulation. These findings strongly suggest that EAAs (versus acetylcholine) mediate fast excitatory synaptic responses of supraoptic neurons to stimulation of cells and axons in the dorsolateral region. The blockade of almost all spontaneous EPSPs by broad-spectrum EAA antagonists likewise argues that EAAs are responsible for the majority of ongoing fast excitatory input, at least from nearby neurons. These responses appear to involve an interaction with kainate and/or quisqualate-type EAA receptors. A preliminary study has been published (Gribkoff and Dudek, 1988), and a longer manuscript is in preparation.

2. Paraventricular nucleus

We have undertaken other studies to test the EAA hypothesis in the paraventricular nucleus. Intracellular recordings (n=4) were obtained from guinea-pig hypothalamic slices in the presence of the GABA_A/Cl⁻ channel antagonist, picrotoxin (50 μ M). Electrical stimuli dorsal to the fornix evoked EPSPs which were averaged every 5 min for 20-30 min in steady state. The mean decrease was 5% for 100 μ M, 44% for 300 μ M and 68% for 1 mM (n=2 each). The effects were reversible (recovery within 45 min after 300 μ M). From the electrophysiological properties, one neuron appeared to be a magnocellular neuropeptidergic cell, but three others had low-threshold calcium spikes (Poulain and Carette, 1987). These data support the hypothesis that EAAs are an important class of transmitter for fast synaptic actions throughout the hypothalamus. These data will be presented at the 1988 Annual Meeting of the Society for Neuroscience (Wuarin and Dudek, 1988).

C. Immunohistochemical differentiation of electrophysiologically distinct neurons in the region of the rat paraventricular nucleus

Neurons with low-threshold calcium spikes (LTS) have been found immediately lateral to

the hypothalamic paraventricular nucleus (Poulain and Carette, 1987). These neurons are distinguishable from non-LTS neurons in the nucleus, not only by the presence of LTS potentials, but also by their afterhyperpolarizations, current-voltage relations and baseline synaptic activity (Tasker and Dudek, 1987). After electrophysiological characterization, LTS and non-LTS neurons were injected with Lucifer yellow and neurophysin immunohistochemistry was performed. Preliminary results showed that 7 of 7 Lucifer-labeled LTS neurons were neurophysin-negative and that 1 of 1 non-LTS neuron was neurophysin-positive. LTS neurons were found to surround the nucleus, including regions that contain CRH cells. From electrical and immunohistochemical data, non-LTS neurons appear to be magnocellular neuropeptidergic cells, whereas LTS neurons probably are not. These preliminary findings support the hypothesis that the two cell types are both physiologically and anatomically distinguishable. These results will be presented at the 1988 Annual Meeting of the Society for Neuroscience (Hoffman, Tasker and Dudek, 1988).

D. Local circuit interactions between neurons in the region of the rat paraventricular nucleus

Local synaptic interactions in the supraoptic and paraventricular nuclei have been postulated on the basis of electrophysiological studies using electrical stimulation to activate presynaptic neurons. This technique stimulates not only local neurons, but also axons projecting from other parts of the brain. We have used glutamate microapplication to stimulate presynaptic neuronal somata and dendrites without activating axons of passage. Neurons in the paraventricular nucleus were recorded intracellularly while glutamate drops (10-100 mM, 50-250 μ m in diameter) were pressure-applied to several locations around the nucleus. Saline drops were applied through a second barrel of the stimulating pipette to control for mechanical effects of drug application. Preliminary results showed that glutamate application, when effective, elicited an increase of EPSPs and/or IPSPs in the recorded neuron. Higher concentrations of glutamate caused trains of PSPs lasting up to several seconds. Picrotoxin (50 μ M) blocked the IPSPs, suggesting they were mediated by GABA_A-receptors. These findings provide electrophysiological evidence for local synaptic interactions in and around the paraventricular nucleus with a technique that is unlikely to involve activation of axons of passage. This method should be useful throughout the mammalian hypothalamus, including the suprachiasmatic nucleus. These data also suggest the hypothesis that local GABAergic neurons regulate the activity of most or all hypothalamic neurons. A presentation of this work will be made at the 1988 Annual Meeting of the Society for Neuroscience (Tasker and Dudek, 1988).

E. Preliminary intracellular recordings from the suprachiasmatic nucleus

We have obtained preliminary intracellular recordings from suprachiasmatic neurons. Electrical stimulation of the optic chiasm evoked EPSPs that were graded with stimulus intensity, and action potentials arose from the larger EPSPs. The quality of intracellular recordings from suprachiasmatic neurons has not been as high as that of other hypothalamic neurons, such as those in the supraoptic and paraventricular nuclei (in terms of input resistance, action potential amplitude, duration of recording, etc.). Nonetheless, our preliminary data are promising. Future work will include studies on the role of excitatory and inhibitory amino acids in synaptic transmission and on local circuit interactions (chemical and electrical) in the suprachiasmatic nucleus.

F. Conclusion

Our studies have provided new evidence regarding the important role of ephaptic interactions in regulating neuronal synchronization in the hippocampus. Other experiments

have documented the importance of EAAs in excitatory synaptic mechanisms of the hypothalamus. This work has also begun to differentiate neuronal subtypes and local circuit interactions in the paraventricular nucleus, a key integrative site of the autonomic nervous system.

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3. PUBLICATIONS

A. Refereed Publications

Dudek, F.E., Gribkoff, V.K., Olson, J.E. and Hertzberg, E.L. (1988) Reduction of dye coupling in glial cultures by microinjection of antibodies against the liver gap junction polypeptide, Brain Res., 439:275-280.

Dudek, F.E., Tasker, J.G. and Wuarin, J.P. (1988) Intrinsic and synaptic mechanisms of hypothalamic neurons studied with slice and explant preparations, J. Neurosci. Meth. (in press, refereed invited chapter).

Gribkoff, V.K. and Dudek, F.E. (1988) The effects of the excitatory amino acid antagonist kynurenic acid on synaptic transmission to supraoptic neuroendocrine cells, Brain Res., 442:152-156.

Gribkoff, V.K. and Dudek, F.E. The effects of excitatory amino acid antagonists on synaptic responses of supraoptic neurons in slices of rat hypothalamus, J. Neurophysiol. (in preparation).

B. Chapters and Symposia

Dudek, F. E. and Christian, E. P. (1987) Inhibition, local excitatory interactions and synchronization of epileptiform activity in hippocampal slices. Ribak, C. E. (Ed.), Inhibition in the Brain, Special Issue of The Journal of Mind and Behavior, 619-633.

Dudek, F. E., Gribkoff, V. K. and Christian, E. P. (1988) Mechanisms of potentiation independent of chemical synapses. Landfield, P. W. and Deadwyler, S. A. (Eds.), Long-Term Potentiation: From Biophysics to Behavior, Alan Liss, New York, 439-464.

Dudek, F. E. and Traub, R. D. Local synaptic and electrical interactions in hippocampus: Experimental data and computer simulations. Berry, W. O. and Byrne, J. (Eds.), Neural Models of Plasticity: Theoretical and Empirical Approaches, Academic Press, (in press).

C. Abstracts

Hoffman, N.W., Tasker, J.G. and Dudek, F.E. (1988) Immunohistochemical differentiation of electrophysiologically distinct neurons in the region of the rat paraventricular nucleus, Soc. Neurosci. Abstr., 14:1178,#470.2.

Tasker, J.G. and Dudek, F.E. (1988) Local circuit interactions between neurons in the region of the rat paraventricular nucleus, Soc. Neurosci. Abstr., 14:1178,#470.3.

Wuarin, J.P. and Dudek, F.E. (1988) Kynurenate antagonism of fast EPSPs in paraventricular neurons, Soc. Neurosci. Abstr., 14:1178,#470.4.

4. PROFESSIONAL PERSONNEL

Dr. Neil Hoffman
Dr. Jian min Li
Dr. Jeffrey Tasker
Dr. Jean-Pierre Wuarin

5. INTERACTIONS

Dr. Dudek presented a paper at the Review of Air Force Sponsored Basic Research in Neuroscience, which was held at the USAF School of Aerospace Medicine, Brooks Air Force Base, Texas (Nov. 30 - Dec. 2, 1987). The title of the presentation was "Electrical Interactions Between Hippocampal Neurons" (abstract enclosed). This meeting provided a means for communication of our work and general discussion with other AFOSR-supported investigators. In particular, we initiated discussions with Dr. Michael Rea concerning the

role of amino acid transmitters in the suprachiasmatic nucleus. This led to the submission by Dr. Martha Gillette of a proposal for a workshop at the Winter Conference Brain Research (WCBR) on this topic entitled "How important are amino acid transmitters in regulating suprachiasmatic neurons of the hypothalamus". (Proposed Participants: M.U. Gillette, M. Rea, A. van den Pol, and F.E. Dudek). Unfortunately, this proposal was not approved, but we still hope to organize this group for collaborative or interactive research on the suprachiasmatic nucleus.

6. NEW DISCOVERIES, INVENTIONS OR PATENT DISCLOSURES--None

7. OTHER STATEMENTS

We have continued to work on electrical interactions between hippocampal neurons, and this report focuses on our most recent research concerning the effects of changes in the osmolality of the extracellular medium on ephaptic interactions. Other studies on electrotonic coupling are still underway. As we have discussed in previous telephone conversations and at the Air Force Neuroscience Review in San Antonio, another major effort has involved the mechanisms of neuronal responsiveness in the hypothalamus. We hope to develop a renewal on this later theme, while still continuing our work on electrical interactions.